

CXXIX.—1 : 3-*Benzodiazolearsinic Acids and their
Reduction Products.*

By ROBERT REGINALD BAXTER and ROBERT GEORGE FARGHER.

SINCE the discovery of salvarsan (Ehrlich and Bertheim, *Ber.*, 1912, 45, 756), many attempts have been made to prepare derivatives or closely allied products which would render unnecessary the somewhat elaborate technique involved in the clinical use of the original compound, which, owing to its pronounced acidity, has to be converted into the disodium salt, in turn alkaline in reaction, before use. Neosalvarsan, the sodium *N*-methylenesulphinate of salvarsan, introduced to avoid these difficulties, possesses many advantages, such as ready solubility and neutral reaction, but, in spite of these, there is a consensus of opinion in favour of salvarsan, as its spirochæticidal action appears to be stronger and more certain.

In this and in other cases the attempts have led to the formation of acid derivatives giving neutral salts with alkalis. The authors desired, on the other hand, to obtain hydrochlorides soluble in water and sufficiently less acid in reaction than salvarsan to admit

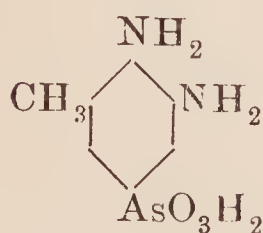
of their direct use, and it was with this object in view that the present investigation was commenced, since it was considered probable that the hydrochlorides of the arsenobenzenes derived from 1:3-benzodiazole (benzoglyoxaline) would fulfil these requirements. Further, considering the properties of the glyoxaline nucleus, they might be expected to exert acidic as well as basic properties, and thus closely resemble salvarsan itself.

Additional interest would attach to such compounds in view of their relationship to 3:4:5:3':4':5'-hexa-aminoarsenobenzene and its *N*-methyl derivatives (D.R.-P. 286667, 286668, 286854, 286855, 294276; E.P. 7488 and 8041 of 1913; U.S.P. 1081079; Benda, *Ber.*, 1914, **47**, 1316; Karrer, *Ber.*, 1916, **49**, 1448), which are stated to possess the unexpected property of dissolving in alkali hydrogen carbonates, forming carbamates with the same degree of alkalinity as that of normal blood serum and a relatively low toxicity (D.R.-P. 269660; E.P. 1667 of 1914).

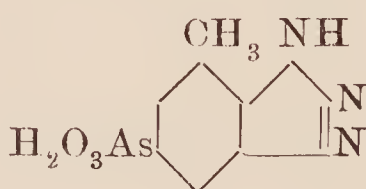
So far as the authors are aware, the benzodiazolearsinic acids have not been examined, Bertheim (*Ber.*, 1911, **44**, 3092), who described 3:4-diaminophenylarsinic acid and several of its derivatives, making no mention of them. They are, however, readily obtained by the well-known reaction of ortho-diamines with formic or acetic acid, whereby the acyl derivative first formed suffers loss of a molecule of water if a monoacyl, or of a molecule of acid if a diacyl derivative, with consequent closing of the ring (compare Ladenburg, *Ber.*, 1875, **8**, 677; Wundt, *Ber.*, 1878, **11**, 826).

The comparative stability of 3:4-diacetylaminophenylarsinic acid, which crystallises from boiling water unchanged, and does not alter save for slight decomposition when heated at 250°/20 mm., and, generally, the stability of diacyl-*o*-diamines (compare Bistrzycki and Ulfers, *Ber.*, 1890, **23**, 1876), seems to indicate that in the absence of anhydrides the reaction proceeds with intermediate formation of a monoacyl derivative.

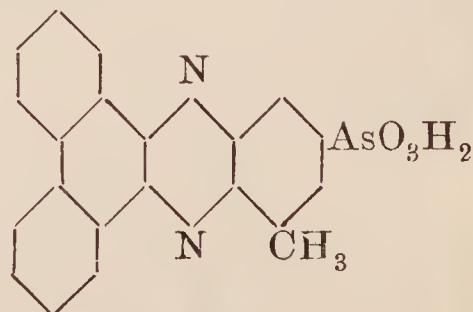
5:6-Diamino-*m*-tolylarsinic acid (I), which, together with 3:4-diaminophenylarsinic acid (Bertheim, *loc. cit.*), formed the starting material for the investigation, was obtained by the reduction of 5-nitro-6-amino-*m*-tolylarsinic acid (this vol., p. 989) with sodium hyposulphite. It undergoes all the condensations typical of an



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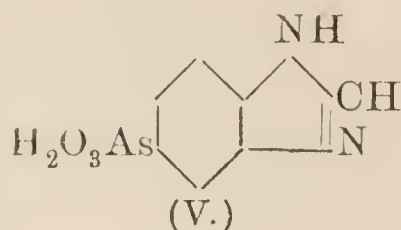
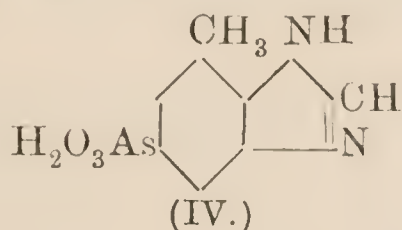
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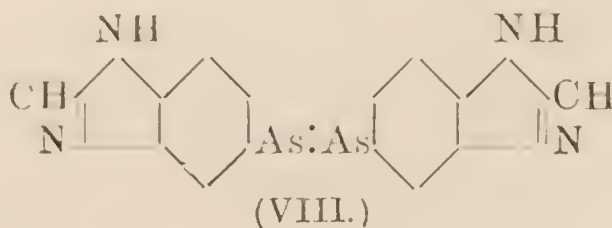
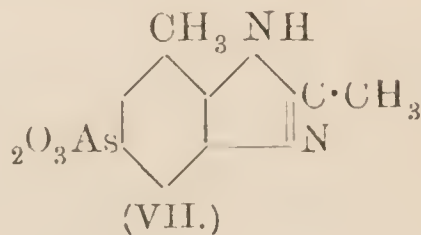
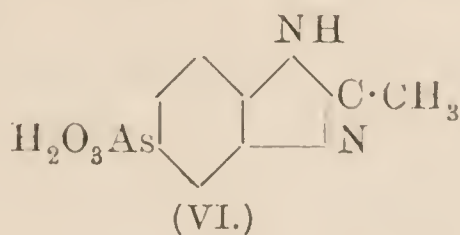
(III.)

o-diamine, giving, for example, with sodium nitrite in acid solution, 7-methyl-1:2:3-benzotriazole-5-arsinic acid (II), and with phenanthraquinone, 4-methylphenanthraphenazine-2-arsinic acid (III). The latter derivative shows the colour reactions characteristic of phenanthraphenazine.

With boiling glacial formic acid, the acids readily yielded 7-methyl-1:3-benzodiazole-5-arsinic acid (IV) and 1:3-benzodiazole-5-arsinic acid (V) respectively.



The action of acetic acid did not proceed quite so smoothly. 3:4-Diaminophenylarsinic acid, although stated (Bertheim, *loc. cit.*) to be readily soluble in acetic acid, is far from being so, and, on boiling with acetic acid, acetic anhydride, or a mixture of the two, gives rise to very highly coloured products, which are difficult to purify. If the reaction is carried out as described in the experimental portion of this paper, the main product is 3:4-diacetylaminophenylarsinic acid, which, on heating with water in a sealed tube at 130°, yields 2-methyl-1:3-benzodiazole-5-arsinic acid (VI). In the case of the higher homologue, the desired reaction takes place predominantly, with the formation of 2:7-dimethyl-1:3-benzodiazole-5-arsinic acid (VII). Incidentally, it may be mentioned that it has since been found that if 3:4-diaminophenylarsinic acid, dissolved in the requisite amount of sodium hydroxide (40 per cent. solution) to form the monosodium salt, is treated with sufficient acetic anhydride to neutralise the sodium hydroxide and form acetic acid with the water present, and then boiled, the main product of the reaction is the benzodiazole derivative.



The reduction of the above acids with hypophosphorous acid, although it proceeds normally, leads to gelatinous products difficult

to handle, and consequently the reduction was carried out by means of sodium hyposulphite. This gives pale yellow *arsenobenzenes*, insoluble in water, which were converted into hydrochlorides by precipitating their solutions in acetic acid with excess of hydrochloric acid, or by treating the suspensions of the bases in water with just sufficient hydrochloric acid to bring about solution, and precipitating as before. The *hydrochlorides* form pale yellow powders, soluble in water, but very sparingly so in the usual organic solvents. Their aqueous solutions react strongly acid to litmus, but neutral to methyl-orange.

It was expected that this acidity would prove too great for purposes of intravenous injection, and that it would be difficult to distinguish between the effect due to the acidity and that due to the arsenic compound. This was confirmed by experiments with 5:5'-*arseno-1:3:1':3'-benzodiazole* (VIII) by Miss Soref, of the Wellcome Physiological Research Laboratories.

EXPERIMENTAL.

3:4-Diaminophenylarsinic Acid.

The preparation of considerable quantities of this acid was carried out according to the directions given by Bertheim (*loc. cit.*), save that it was found advisable to omit the boiling of the solution after the reduction with sodium hyposulphite, as this diminished the yield and gave a more highly coloured product.

1:3-Benzodiazole-5-arsinic Acid (V).

Ten grams of 3:4-diaminophenylarsinic acid were boiled under a reflux condenser for six hours with 100 c.c. of glacial formic acid. After removal of the excess of formic acid by distillation, water was added, when 7.5 grams of crystalline material rapidly separated. To remove adhering traces of colouring matter, the product was treated with charcoal in dilute alkaline solution. On making neutral to methyl-orange, crystallisation commenced at once, practically the whole being recovered in a pure state.

1:3-Benzodiazole-5-arsinic acid crystallises from water, in which it is sparingly soluble, in clusters of minute, flattened prisms, which are anhydrous. On heating, it gradually darkens above 250° and decomposes rapidly about 297° (corr.).

Found: N=11.4; As=30.8.

C₇H₇O₃N₂As (242.1) requires N=11.6; As=30.96 per cent.

5:5'-Arseno-1:3:1':3'-benzodiazole (VIII).

A solution of 5 grams of 1:3-benzodiazole-5-arsinic acid in 100 c.c. of water containing 1.2 grams of sodium hydroxide was treated with 50 grams of sodium hyposulphite and 11.5 grams of magnesium chloride dissolved in 300 c.c. of water, and the mixture heated, with stirring, at 60° for two hours in an atmosphere of carbon dioxide, by which time the precipitation of the yellow arsenobenzene was complete. After cooling, the product was collected, well washed with water, suspended in 90 c.c. of water, dissolved by the addition of sufficient hydrochloric acid to form the dihydrochloride, filtered from traces of undissolved matter, and precipitated by pouring into an equal volume of concentrated hydrochloric acid. The hydrochloride was collected, well washed with alcohol and ether, and dried in a vacuum over sulphuric acid. The yield amounted to 3.9 grams.

5:5'-Arseno-1:3:1':3'-benzodiazole is obtained as a bright yellow powder practically insoluble in water or the usual organic solvents, sparingly, if at all, soluble in methyl alcohol containing hydrochloric acid, but fairly readily so in 50 per cent. acetic acid. The *dihydrochloride* forms a pale yellow powder soluble in water, very sparingly so in methyl alcohol or ethyl alcohol, and quite insoluble in acetone or ether. The aqueous solution reacts acid to litmus, but neutral to methyl-orange. After drying in a vacuum overnight, it retains solvent equivalent to two molecules of water.

Found: N=11.3; As=30.2; Cl=13.8.

$C_{14}H_{10}N_4As_2, 2HCl, 2H_2O$ (493.1) requires N=11.4; As=30.4; Cl=14.4 per cent.

3:4-Diacetylaminophenylarsinic Acid and 2-Methyl-1:3-benzodiazole-5-arsinic Acid (VI).

Experiments in which diaminophenylarsinic acid was heated with glacial acetic acid, with acetic anhydride, with acetyl chloride and pyridine, or with acetic anhydride in the presence of a trace of sulphuric acid, were unsuccessful, owing to the considerable amount of decomposition which occurred. It was found, however, that if the acid, dissolved in methyl alcohol, was treated with a mixture of acetic acid and acetic anhydride, and the methyl alcohol then removed as completely as possible by distillation on the water-bath, the resulting solution, after heating to active boiling for four hours, gave an excellent yield of a product, which, from its composition, proved to be the diacetyl derivative of diaminophenylarsinic acid.

3:4-Diacetylaminophenylarsinic acid crystallises from water, in

which it is fairly readily soluble, as a felted mass of fine needles which retain from 2 to 2.5 per cent. of solvent.

Found: loss at 110° (two specimens) 2.6, 2.2.

In dried material: $N=8.8$; $As=23.8$.

$C_{10}H_{13}O_5N_2As$ (316.1) requires $N=8.9$; $As=23.7$ per cent.

As the product did not lose acetic acid when heated to $250^{\circ}/20$ mm., it was heated with ten times its weight of water in a sealed tube for four hours at 130° , when the desired reaction took place almost completely.

2-Methyl-1:3-benzodiazole-5-arsinic acid crystallises from water, in which it is somewhat sparingly soluble, in minute needles containing two and a-half molecules of water of crystallisation, the last half molecule being removed with difficulty at 110° , but fairly readily at 120° . After drying at 110° , it darkens on heating above 250° and decomposes at about 270° (corr.).

Found: loss at $110^{\circ}=15.5$.

$C_8H_9O_3N_2As, 2\frac{1}{2}H_2O$ requires $H_2O=15.0$ per cent.

In dried material: $C=37.3$; $H=3.8$; $N=10.7$; $As=29.3$.

$C_8H_9O_3N_2As$ (256.1) requires $C=37.5$; $H=3.5$; $N=10.9$; $As=29.3$ per cent.

2:2'-Dimethyl-5:5'-arseno-1:3:1':3'-benzodiazole.

This was prepared in the same manner as 5:5'-arseno-1:3:1':3'-benzodiazole, which it resembles very closely in its properties.

The *dihydrochloride* forms a pale yellow powder, soluble in water, but almost completely insoluble in methyl alcohol, ethyl alcohol, ether, or acetone. After drying in a vacuum for twenty-four hours, it retains solvent approximating to three molecules of water. In aqueous solution it reacts acid to litmus but neutral to methyl-orange.

Found: $N=10.3$; $Cl=12.7$; $As=28.0$.

$C_{16}H_{14}N_4As_2, 2HCl, 3H_2O$ (539.1) requires $N=10.4$; $Cl=13.1$; $As=27.8$ per cent.

5:6-Diamino-m-tolylarsinic Acid (I).

A solution of 8.6 grams of 5-nitro-6-amino-*m*-tolylarsinic acid in 75 c.c. of water and 6.2 c.c. of 10*N*-sodium hydroxide was cooled to -1° and treated, in one operation, while stirring vigorously, with 20.4 grams of sodium hyposulphite. When the reaction was complete, as shown by the change in colour, the solution was filtered, treated with 8.1 c.c. of hydrochloric acid (D 1.12), and the resulting acid, which separated in the course of a few minutes,

collected, washed with water, and recrystallised from water, in which it is sparingly soluble in the cold, but fairly readily so on warming. It separates in colourless needles, which contain between one and a-half and two molecules of water of crystallisation. It dissolves fairly readily in methyl alcohol or acetic acid, but is very sparingly soluble in ether, benzene, or petroleum. Its solution in dilute hydrochloric acid gives a characteristic, deep violet coloration with a drop of a dilute solution of potassium dichromate. It appears to decompose slowly on keeping.

Loss at $110^{\circ} = 11.2$.

$C_7H_{11}O_3N_2As, 1\frac{1}{2}H_2O$ requires 9.9 per cent.

$C_7H_{11}O_3N_2As, 2H_2O$ requires 12.8 per cent.

In dried material: $N = 11.3$; $As = 30.4$.

$C_7H_{11}O_3N_2As$ (246.1) requires $N = 11.4$; $As = 30.5$ per cent.

7-Methyl-1:2:3-benzotriazole-5-arsinic acid (II) was obtained by treating a solution of 3:4-diamino-*m*-tolylarsinic acid in dilute hydrochloric acid with a molecular proportion of sodium nitrite. It forms a crystalline powder very sparingly soluble in water, but more readily so in alcohol. It crystallises from 50 per cent. alcohol in minute, colourless, glistening needles, which are anhydrous, and gradually decompose on heating above 280° .

Found: $N = 16.6$.

$C_7H_8O_3N_3As$ (257.1) requires $N = 16.4$ per cent.

4-Methylphenanthraquinazoline-2-arsinic acid (III) was obtained by the condensation of molecular proportions of phenanthraquinone and 3:4-diamino-*m*-tolylarsinic acid in acetic acid solution. It forms an amorphous, yellow powder, sparingly soluble in water and the usual organic solvents. With concentrated sulphuric acid, it develops an eosin-red colour, with nitric acid a cherry-red, and with hydrochloric acid an insoluble red compound. The colour is discharged in all three cases by dilution with water. It dissolves in dilute sodium carbonate or sodium hydroxide, but a flocculent precipitate of the sodium salt is thrown down on the addition of excess of the reagent.

Found: $N = 6.4$.

$C_{21}H_{15}O_3N_2As$ (418.2) requires $N = 6.7$ per cent.

7-Methyl-1:3-benzodiazole-5-arsinic Acid (IV).

Two grams of 3:4-diamino-*m*-tolylarsinic acid were boiled with 20 c.c. of glacial formic acid for six hours. The isolation of the product was carried out as in the case of 1:3-benzodiazole-5-arsinic acid, save that the treatment with charcoal was found to be more

effective in acid solution. The air-dried product contains only traces of moisture and resembles the lower homologue very closely in its properties. It dissolves sparingly in water and crystallises in minute, prismatic needles, which darken when heated above 280° and melt and decompose at about 300° (corr.).

Found: loss at $110^{\circ}=1.3$.

In dried material: $N=10.8$; $As=29.4$.

$C_8H_9O_3N_2As$ (256.1) requires $N=10.9$; $As=29.3$ per cent.

7:7'-Dimethyl-5:5'-arseno-1:3:1':3'-benzodiazole.

This was obtained by the reduction of the above acid with sodium hyposulphite in the manner previously described (p. 1376), as a pale yellow powder, insoluble in water and the usual organic solvents, but moderately soluble in acetic acid. The corresponding *dihydrochloride* forms a pale yellow, granular powder soluble in water, but insoluble in methyl alcohol, ethyl alcohol, ether, or acetone. After drying for twenty-four hours under greatly reduced pressure, it retained solvent corresponding with two molecules of water.

Found: $N=10.6$; $As=28.6$; $Cl=13.1$.

$C_{16}H_{14}N_4As_2 \cdot 2HCl \cdot 2H_2O$ (521.1) requires $N=10.75$; $As=28.8$; $Cl=13.6$ per cent.

2:7-Dimethyl-1:3-benzodiazole-5-arsinic Acid (VII).

This acid was obtained by the prolonged action (six to eight hours) of boiling acetic acid on 5:6-diamino-*m*-tolylarsinic acid, the isolation being carried out in the usual manner. It is somewhat soluble in boiling water, but sparingly so in cold, and separates from the former in minute, prismatic needles which contain two molecules of water of crystallisation.

Found: loss at $110^{\circ}=12.2$.

$C_9H_{11}O_3N_2As \cdot 2H_2O$ requires 11.8 per cent.

In dried material: $N=10.6$; $As=27.9$, 27.5.

$C_9H_{11}O_3N_2As$ (270.1) requires $N=10.4$; $As=27.75$ per cent.

2:7:2':7'-Tetramethyl-5:5'-arseno-1:3:1':3'-benzodiazole.

The above acid was readily reduced to the corresponding arsenobenzene by sodium hyposulphite, under the conditions previously employed. The *arsenobenzene* closely resembles those already described in its physical and chemical properties. The *dihydrochloride* forms a pale yellow powder soluble in water, but insoluble

in the usual organic solvents. After drying for twenty-four hours in a vacuum, it retains solvent corresponding with approximately two molecules of water.

Found: $N=10.0$; $As=27.3$; $Cl=12.3$.

$C_{18}H_{18}N_4As_2, 2HCl, 2H_2O$ (549.1) requires $N=10.2$; $As=27.3$;
 $Cl=12.9$ per cent.

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